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(54) Title: USE OF PHOTOPHERESIS IN THE TREATMENT OF CHRONIC INFECTION BY HEPATITIS C VIRUS

(57) Abstract

A method of treating chronic hepatitis C virus infection in a patient by photopheresis alone, or in combination with interferon therapy is provided.

USE OF PHOTOPHERESIS IN THE TREATMENT OF CHRONIC INFECTION BY HEPATITIS C VIRUS

BACKGROUND OF THE INVENTION

Acute viral hepatitis is a systemic infection predominantly affecting the liver. Six categories of viral agents including hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), hepatitis E virus (HEV) and hepatitis G virus (HGV) have been implicated as causing this disease. HBV, HCV, HDV and HGV can all result in chronic liver disease. While these agents can be distinguished based upon their antigenic properties, they produce clinically similar illnesses. These range from asymptomatic and inapparent to fulminant and fatal acute infections and from subclinical persistent infections to progressive chronic liver disease with cirrhosis and hepatocellular carcinoma.

Hepatitis C virus, formerly referred to as non-A, non-B hepatitis virus, was first identified in patients exhibiting incubation periods and modes of transmission consistent with hepatitis infections, without serological evidence of hepatitis A or B. An RNA virus with immunologic specificity for transfusion-associated non-A, non-B viral hepatitis was identified in 1988. The introduction of anti-HCV assays has reduced the frequency of transfusion-associated hepatitis C, however, this virus can be transmitted via other percutaneous routes such as self-injection with intravenous drugs. In addition this virus can be transmitted by occupational exposure to blood, and the likelihood of infection is increased in

hemodialysis units. While the frequency of transfusion-associated hepatitis C has decreased, the overall frequency of hepatitis C has remained the same, primarily because of increases in other modes of transmission. The risk of HCV infection is also increased in organ transplant recipients and in patients with AIDS. Chronic hepatitis C virus infections occurs in as many as 20% of renal transplant recipients. Regardless of the mode of acquisition of HCV infection, chronicity follows acute hepatitis C virus in approximately 80% of the cases. Further, in patients with chronic transfusion-associated hepatitis followed for 10 years, progression to cirrhosis has been recorded in 20%. This has been observed even in patients with relatively mild symptoms and even asymptomatic patients with a history of acute hepatitis C virus infection.

The physiological mechanisms that allow establishment of chronic hepatitis C virus (HCV) infection following acute HCV infection are not known, although immune system mechanisms are the focus of most research. Some researchers have suggested that impaired cellular immunity, involving either T cells or natural killer cells, may play a role in the evolution of chronic infection with HCV. There is no specific treatment for typical acute viral hepatitis of the HCV type. Antiviral therapies such as interferon alpha, a drug that has both direct antiviral effects as well as acting as a modulator of immune system functions in response to infection, has been shown to be effective in only a proportion of patients (Hayden, F.G., *Antiviral agents*, pp. 1211-1213, In: Hardman et al., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 1996, McGraw Hill, New York). For example, treatment of chronic HCV with interferon alpha-2b (Intron-A), an FDA-approved therapy for chronic HCV infection, has only a 8-20% success rate.

Some researchers have suggested that rapid mutation within the hypervariable region of the HCV genome may explain a loss of immune recognition and clearance of HCV (Weiner et al., *Proc. Natl. Acad. Sci.*, 1992, 89:3468-3472). There is some evidence that the genotype of the virus itself may be

important in influencing therapeutic outcomes with immunotherapeutics such as interferon (Simmonds, P. *Hepatology*, 1995, 21:571-583); some genotypes of HCV may be more resistant to therapy with interferon alpha. Still, the basic immune mechanisms responsible for clearance of HCV are not known.

HCV is a positive-strand virus that replicates by producing negative-strand RNA as a template. During active HCV viral replication, these negative-strand RNA templates are present in the patient's liver. Investigators have also found active, replicating HCV particles in patients' peripheral blood mononuclear cells (PBMCs). Monocytes, macrophages, T-cells, and B-cells have all been shown to contain negative-strand HCV RNA (Zignego et al., *J. Hepatol.*, 1992, 15:382-386).

During therapy with interferon-alpha, HCV disappears from the patient's liver and blood. Despite this apparent clearance of virus, there is a very high (80-85%) relapse rate after interferon therapy. Investigators have found that the patients who do not have HCV replication detected in their PBMCs at the end of therapy with interferon-alpha do not relapse and are apparently "cured" (Quian et al., *J. Hepatol.*, 1992, 16:380-383; Gil et al., *Hepatology*, 1993, 18:1050-1054). These data suggest that the mononuclear cell serves as an immunologically protected site that shelters HCV from immune system recognition and attack. As a result, once interferon-alpha therapy is withdrawn, the virus is able to leave the PBMCs and reinfect the patient's blood and liver. Ideal therapy for HCV would clear the virus from the liver, blood, and infected mononuclear cells simultaneously.

Extra-corporeal photopheresis (photopheresis) causes an immunization of the host body to abnormal T-cells. The method uses ultraviolet light to damage abnormal T-cells rendering them more immunogenic. After photopheresis treatment, reinfusion of these altered T-cells causes an immunologic reaction that targets the unirradiated T-cells carrying the same surface antigens (Edelson, R.L., *Ann. NY Acad. Sci.*, 1991, 636:154-164). This results in production of a highly specific

immune response against these abnormal cells. Photopheresis has been used successfully to treat a variety of diseases involving abnormal immune system function such as T cell lymphoma, pemphigus vulgaris and progressive systemic sclerosis, lupus erythematosus, rheumatoid arthritis acquired immunodeficiency syndrome (AIDS)-related complex (Edelson, R.L., *Yale J. Biol. Med.*, 1989, 62:565-577, Edelson et al. *N. Engl. J. Med.*, 1987, 316(6):297-303; Knobler, R.M. et al., *J. Am. Acad. Dermatol.*, 1993, 28:580-584; Bisaccia, E. et al., *J. Acquir. Immune Defic. Syndr.*, 1993, 6:386-392; Bisaccia, E. et al., *Ann. Int. Med.*, 1990, 113:270-275; Abrutyn, E., *Ann. Int. Med.*, 1990, 113:263-264). Additional diseases for which this treatment is proposed include multiple sclerosis and organ transplant rejection.

In the present invention, photopheresis is used in the treatment of chronic hepatitis C virus infection, either alone or in combination with interferon.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a method of treating a patient chronically infected with hepatitis C virus which comprises administering to the infected patient a photoactive compound and subsequently exposing blood from the patient to electromagnetic radiation so that any photoactive compound in the blood is activated. This method can also be combined with interferon therapy in the treatment of chronic hepatitis C virus infections.

DETAILED DESCRIPTION OF THE INVENTION

Photopheresis is the process by which peripheral blood is exposed in an extracorporeal flow system to a photoactivated psoralen compound such as 8-methoxypsoralen (8-MOP). Photoactivation is achieved by use of electromagnetic radiation such as ultraviolet A light. Photopheresis, which is now approved by the Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphomas (mycosis fungicides, Sezary Syndrome and related presentations), is showing

substantial promise in a variety of autoimmune disorders. Edelson et al. *The Yale Journal of Biology and Medicine* **1989**, 62:565-577. Additional diseases for which clinical trials are in progress include multiple sclerosis, organ transplant rejection, rheumatoid arthritis and AIDS. Photopheresis is now used routinely as an adjunct therapy with radiotherapy in the treatment of cutaneous tumors. Photopheresis is also being used to attenuate retroviruses such as HIV and/or kill blood cells which have been infected with a retrovirus. U.S. Patent 4,960,408.

Photoactivated-MOP initiates a cascade of immunologic events by forming covalent photoadducts with nuclear and cell surface adherent DNA and possibly with other cellular molecules. Photopheresis increases the immunogenicity of the irradiated T cells so that their reinfusion induces a therapeutically significant immunologic reaction that targets unirradiated T cells of the pathogenic clones. Human T cells have been shown to be quite sensitive to the combined effects of 8-MOP and UVA. Morison et al., *Clin and Expt'l Dermatol.* 1981, 6:273-277; Khavari et al., *Clin. Res.* 1988, 36(3):662A.

This extracorporeal procedure, known as photopheresis, and apparatus for performing this procedure were first developed by engineers at Therakos, Inc. (Westchester, PA), a subsidiary of Johnson and Johnson, Inc. The equipment combines an initial centrifugation step to enrich the blood for lymphocytes with an ultraviolet exposure system.

In the present invention, a method is provided wherein a patient infected with hepatitis C virus is treated by administering an effective amount of a photoactive compound to a patient's blood and subsequently activating the photoactive compound in the blood by exposure to an adequate amount of electromagnetic radiation. A photoactive compound is first administered to the blood of a patient infected with hepatitis C virus. The photoactive compound can be administered *in vivo*, either orally or intravenously. Alternatively, the photoactive compound is administered *in vitro* to a portion of the patient's blood which has been removed from the patient by conventional

blood withdrawal techniques. The portion of the patient's blood to which the photoactive compound has been administered is then treated by subjecting that portion to photopheresis using electromagnetic radiation. In a preferred embodiment, the electromagnetic radiation is ultraviolet light, most preferably long wavelength ultraviolet light (UVA) at a wavelength within the range of 320 to 400 nm. It is preferred that the photopheresis step be carried out *in vitro* using an extracorporeal photopheresis apparatus. When the photopheresis step is performed *in vitro*, a portion of the treated blood is returned to the patient following the photopheresis. Photopheresis may also be performed *in vivo*.

Psoriasis patients have been shown to readily tolerate 50 to 200 ng of 8-MOP per milliliter of blood. Gilchrestet al. *Cancer* 1976, 38:683-689. Cell division by T cells can be blocked almost completely by 1 to 2 joules per square centimeter of UVA energy in the presence of 100 ng 8-MOP. Because of the weakness of the UVA energy, exposure is performed on a very thin film of blood. For example, in clinical trials for CTCL, blood is passed at a film thickness of only 1 millimeter between two high intensity UVA energy sources, translating to a maximal distance between the targeted T cells and the light of only 0.5 millimeters. In this treatment, the total volume of patient blood outside the body during the treatment is approximately one unit or 500 milliliters. In these studies, it was determined that 150 minutes of UVA exposure in the photopheresis apparatus were necessary to reach 2 joules per square centimeter of irradiation. Photopheresis on two successive days at monthly intervals, which permits irradiation of less than 10% of the total body burden of malignant cells in a patient with CTCL, resulted in 4 out of 5 patients responding after only 6 to 10 treatments.

Accordingly, dosages to be administered in the present invention can be routinely determined by one of skill in the art. Preferred dosages range from about 0.3 to about 0.8 mg/kg. Knobler et al., *J. Am. Acad. Dermatol*. 1993, 18:580-

584. When administered to the patient's blood *in vivo*, it is preferred that the photoactive compound be administered orally, although intravenous or other conventional routes of administration can be used. When administered orally, it is preferred that the photoactive compound be administered at least one hour prior to photopheresis but no more than three hours prior to photopheresis. When administered intravenously, these times may be shorter. The exposure to ultraviolet light during the photopheresis is preferably from about 3 to about 4 hours, although shorter or longer periods may be used. It is preferred that this treatment be performed at weekly intervals. Treatment has continued in some instances for up to 18 months (Edelson, R. et al., *N. Engl. J. Med.* 1987, 316:297-303; Edelson, R., *Yale J. Biol. Med.* 1989, 62:565-577; Wilfert, H. et al., *Br. J. Dermatol.* 1990, 122:225-232).

Photoactive compounds which can be used in the present invention must be capable of binding to nucleic acids upon exposure to electromagnetic radiation such as ultraviolet light. Preferred photoactive compounds include compounds known as psoralens which are described in U.S. Patent 4,321,919. Examples of these preferred compounds include, but are not limited to, psoralen, 8-methoxypsoralen, 4,5'8-trimethylpsoralen, 5-methoxypsoralen, 4-methylpsoralen, 4,4'-dimethylpsoralen, 4,5'-dimethlypsoralen and 4',8-methoxypsoralen.

The method of the present invention for the treatment of hepatitis C virus by photopheresis can also be used in combination with interferon therapy. The use of interferon in the treatment of viral infections is well known in the art. Interferon has been shown to be effective in treating hepatitis C virus in clinical trials at doses ranging from 1-6 million units (MU), 3 times per week for 2-18 months (Tine, F. et al., *J. Hepatol.* 1991, 13:192-199; Weiland, O. and R. Scharcz, *Scand. J. Gastroenterol.* 1992, 27:337-342; Reichard, O. et al., *Hepatology* 1994, 19:280-285; Poynard, T. et al., *N. Engl. J. Med.* 1995, 332:1457-1462; Boucher, E. et al., *Hepatology* 1995, 21:322-327). Because of the low (8-20%) success rate of

interferon therapy for chronic HCV, it is recognized by physicians that there is a critical need to evaluate combination therapies where interferon is used in conjunction with other putative agents (Boucher et al., *Hepatology* 1995, 21:322-327). It is now believed that interferon therapy in combination with photopheresis is an effective method for treatment of hepatitis C virus. When interferon has been used in combination with other drugs for treatment of hepatitis C virus (Boucher et al., *Hepatology* 1995, 21:322-327), there was no change in the interferon dosing regimen from that which was used as a standard therapy, i.e., 3 MU, 3 times/week for 6 months. Further, interferon therapy has been given safely to patients in combination with photopheresis to treat cutaneous T-cell lymphoma (Roenigk, H.H. et al., *J. Invest. Dermatol.* 1990, 95:198S-205S); the researchers combined an aggressive interferon regimen (6 to 30 MU, 3 times/week, for an indefinite period) with a standard photopheresis regimen (0.6 mg photoactive agent, with treatment 2-3 times each week, every two weeks or monthly until lesions cleared). As a result, dosages to be administered in the present invention would be in the range of 1-6 MU interferon, 3 times each week, for up to 18 months. Photoactive compound would be administered intravenously or orally at doses in the range of 0.3 to 0.8 mg/kg (Knobler et al., *J. Am. Acad. Dermatol.* 1993, 28:580-584), approximately one hour before initiating photopheresis. The photopheresis procedure itself can be administered as often as 2 to 3 days each week or monthly, depending on the clinical response.

The following non-limiting examples are provided for illustrative purposes only.

EXAMPLES

Example 1 Initial Clinical Application of Photopheresis Treatment in Chronic HCV Infection

Initial clinical trials would include from 30 to 50 patients (at least 10 per group) selected based on the following criteria:

- histopathological evidence of chronic active HCV by liver biopsy
- seropositivity for anti-HCV antibodies (by ELISA and PCR); negative for HBV surface antigen
- presence of abnormal ALT levels in serum for more than 6 months
- no recent history of alcohol or drug abuse
- no immunosuppressant or antiviral therapy within the last 6 months
- no evidence of other liver diseases, cancer, HIV infection, renal disease, cardiovascular disease, neurological disease, or gastrointestinal disease

Each of these inclusion/exclusion criteria are typically employed in clinical studies of hepatitis therapies (Main, J., *J. Hepatol.*, 1995, 23:32-36; Boucher, E., *Hepatology*, 1995, 21:322-327; Poynard, T. et al., *New Engl. J. Med.*, 1995, 332:1457-1462). Patients will be randomly assigned to one of three treatment groups: i) photopheresis alone, 2) interferon-alpha alone (where interferon-alpha is the current standard of care therapy for HCV infection), or 3) photopheresis in combination with selected doses of interferon-alpha.

Patients receiving photopheresis alone are administered a standard dose of photoactive compound either intravenously or orally (0.3 to 0.8 mg/kg; chosen at the discretion of the investigator), approximately one hour before initiating photopheresis. The photoactive compound can also be administered directly into the leukocyte/plasma concentrate in the treatment bag of the photopheresis apparatus before irradiation with UVA light. The photopheresis treatment is repeated two times each week for 6 months. Patients are then followed for an additional 6 months to assure long-term HCV clearance. Blood samples are taken weekly during the treatment period (first 6 months), and then every month for the 6 month follow-up period. The clinical endpoints monitored through blood sampling include: 1) levels of HCV RNA, 2) serum alanine aminotransferase (ALT) levels, 3) total bilirubin levels, 4) prothrombin time, 5) alkaline phosphatase levels, 6) presence

of HBV antibodies, and 7) routine hematological and serum chemistry parameters. Response to treatment will be determined by 1) return of ALT values to normal for the 6 month follow-up, and 2) negative results for HCV RNA for 6 months after therapy is completed.

Patients receiving interferon-alpha treatment alone receive intramuscular injections , 3 times each week (3 million units; a standard regimen as described by: Main, J., 1995; Lampertico, P. et al., *Hepatology*, 1994, 19:19-22; Boucher, E. et al., 1995; Rasi, G. et al., *Gut*, 1996, 39:679-683; Reichard, O. et al., *Hepatology*, 1994, 19:280-285). Interferon treatment will continue for 6 months, with a 6 month follow-up to determine if HCV clearance is sustained. The same inclusion/exclusion criteria are applied to this group, as were discussed above for photopheresis therapy alone; the same blood sampling protocol also is employed (identical endpoints).

Patients receiving photopheresis treatment in combination with interferon treatment receive the photopheresis regimen described above as well as intramuscular injections of selected doses of interferon-alpha, 3 times each week. Interferon treatment and photopheresis treatment continues for 6 months, with a 6 month follow-up to determine if HCV clearance is sustained. The same inclusion/exclusion criteria are applied to the combination therapy group, and the same blood sampling protocol is employed (identical endpoints).

At the end of the 6 months treatment, the clinical signs and symptoms of patients in all treatment groups are ascertained. Successful treatment or "efficacy" is established by patients exhibiting decreased levels of ALT in serum (as compared to levels ascertained at the beginning of treatment) and decreased levels of HCV RNA (as compared to levels ascertained at the beginning of treatment). Other studies with interferon alone are available for comparison of response rates in this initial trial (Reichard, O. et al. 1994; Diodati, G., et al., *Hepatology*, 1994, 19:1-5; Poynard, T. et al., 1995, *supra*). Typical long-term response rates in these studies are in the range of 40%.

Example 2 Safe Clinical Application of Photopheresis Treatment in Combination with Interferon-Alpha

Maximum tolerated doses of interferon when combined with photopheresis therapy have been determined. Although the disease state treated was cutaneous T-cell lymphoma, the results provide important information on the utility of such a combination treatment in a disease state where interferon is one of the standard therapies that is used singly (Jorg, B. et al., *Dermatol. Clin.*, 1994, 12:433-441).

Interferon-alpha 2a was administered three times weekly by intramuscular injection to 15 patients with histologically confirmed mycosis fungoides (one of the forms of cutaneous T-cell lymphomas). Initial dose levels of interferon were between 6 and 30 MU, with an escalation of the dose over a two month period. Photopheresis therapy was initiated concurrently; 0.6 mg/kg of 8-MOP was given orally two hours before treatment. Photochemotherapy treatment was given 2 to 3 times every week for 2 weeks, every 2 weeks for 8 weeks, and then every 4 weeks for 8 weeks. This photopheresis regimen was the same as was given to a comparison group of patients receiving only photopheresis treatment. The results showed that there was no reported unusual toxicity from what was seen in patients receiving interferon alone.

Example 3 Optimization of Photopheresis Treatment for Chronic HCV Infection

Upon completion of initial clinical studies, the therapy will be optimized for maximum effect and long-term therapy. Published studies with interferon-alpha therapy in chronic HCV infection indicate that some patients may require treatment for up to 18 months to assure long-term viral clearance or "cure" (Poynard, T. et al. 1995, *supra*). Further, patients with cirrhotic liver disease would be candidates for therapy once initial trials have been completed successfully.

In this optimization phase, photopheresis treatment is employed both alone and in combination with interferon alpha. Photoactive compound is administered orally at doses as high as

0.8 mg/kg, 3 times each week for varying times (from 6 months to 18 months), with at least a 6 month follow-up period after cessation of treatment. Alternatively, photoactive compound could be added directly to the collection bag. Combination therapy with interferon-alpha also continues for up to 18 months, with similar time point groups included. At least 7 patients would be included in each time point group, for each treatment regimen. Inclusion/exclusion criteria could be relaxed in these trials to include subgroups of patients with evidence of cirrhosis or the presence of HBV surface antigen. Response to therapy is determined as described in Example 1 (normal serum ALT values and negative HCV RNA).

What is Claimed:

1. A method of treating chronic hepatitis C virus infection in a patient comprising administering to the patient a photoactive compound and subsequently exposing blood from the patient to electromagnetic radiation so that any photoactive compound in the blood is activated.

2. The method of claim 1 wherein the photoactive compound comprises 8-methoxypsoralen.

3. The method of claim 1 wherein the electromagnetic radiation is ultraviolet A light.

4. The method of claim 1 further comprising administering interferon therapy to the patient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/05966

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/35
US CL :514/455
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/455

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS
search terms: 8-methoxypsoralen, psoralen, MOP, hepatitis C, HCV

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,399,719 A (WOLLOWITZ et al) 21 March 1995, col. 2, lines 43-68.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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02 JUNE 1997	10 JUL 1997
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